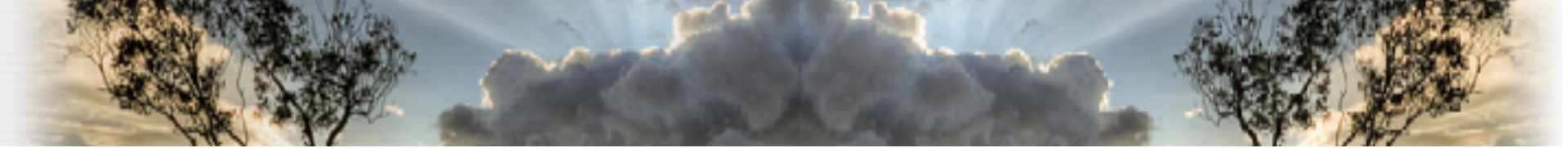

Context of Use versus the BMV - why the discussion?

Biomarkers and CoU: an uphill journey for young scientists?

June 11th, 2021

Kyra Cowan

PK COU vs. Biomarker COU

2012: EBF Recommendation Paper

WHITE PAPER

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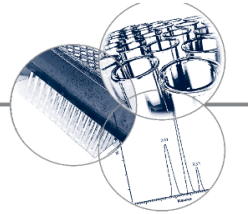

European Bioanalysis Forum recommendation on method establishment and bioanalysis of biomarkers in support of drug development

Biomarkers have become increasingly important in drug development and many bioanalysts are getting involved. Consequently, different views on how to approach the bioanalysis of biomarkers have been published or are being developed. The European Bioanalysis Forum has intensively discussed this topic since 2010 and is ready with their recommendation on method establishment and bioanalysis of biomarkers. Acknowledging that the challenges step outside the bioanalytical laboratory is a cornerstone of our recommendation. The importance of integrating all scientific aspects, from purely analytical aspects, all the way to understanding the biology and effects of the biomarker, prior to embarking on method establishment or sample analysis, cannot be underestimated. Close and iterative interactions with the teams requesting the data is imperative to develop a bioanalytical strategy that combines science, analytical performance and regulations. The European Bioanalysis Forum developed a straightforward decision tree to help the scientific community in developing a bioanalytical strategy for any biomarker in drug development.

1. Introduction & scope

In this manuscript, the European Bioanalysis Forum (EBF) reports back from their internal discussions on the method establishment and bioanalysis of biomarkers in support of drug development performed in the regulated bioanalytical environment. Initially, these discussions were an integral part of an EBF subteam assigned to provide a recommendation on the (bio)analytical community's approach to biomarker bioanalysis [3]. Nevertheless, although the latter paper provides excellent insight into the science of how to approach biomarker bioanalysis, the EBF experienced that the industry was moving forward too often to analyze biomarkers using existing regulated bioanalysis standards [4,103–105] or remained confused on fully embracing the opportunities and tiered

Philip Timmerman*[1], Christian Herling[2], Daniela Stoellner[3], Birgit Jaitner[3], Susanne Pihl[4], Karen Elsby[5], Neil Henderson[5], Begona Barroso[6], Stephanie Fischmann[7], Arjen Companjen[8], Amanda Versteilen[8], Stewart Bates[9], Clare Kingsley[10]

Bioanalysis (2012); 4(15): 1883–94

EBF

2020

White Paper

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Bioanalysis

Update to the European Bioanalysis Forum recommendation on biomarkers assays; bringing context of use into practice

Joanne Goodman[1], Kyra J Cowan[2], Michaela Golob[3], Lars Karlsson[4], Ulrich Kunz[5], Robert Nelson[6], Hans Ulrichts[7], Lauren Stevenson[8], Linda Terry[9] & Philip Timmerman*,[10]

Bioanalysis (2020) 12(20), 1427–1437

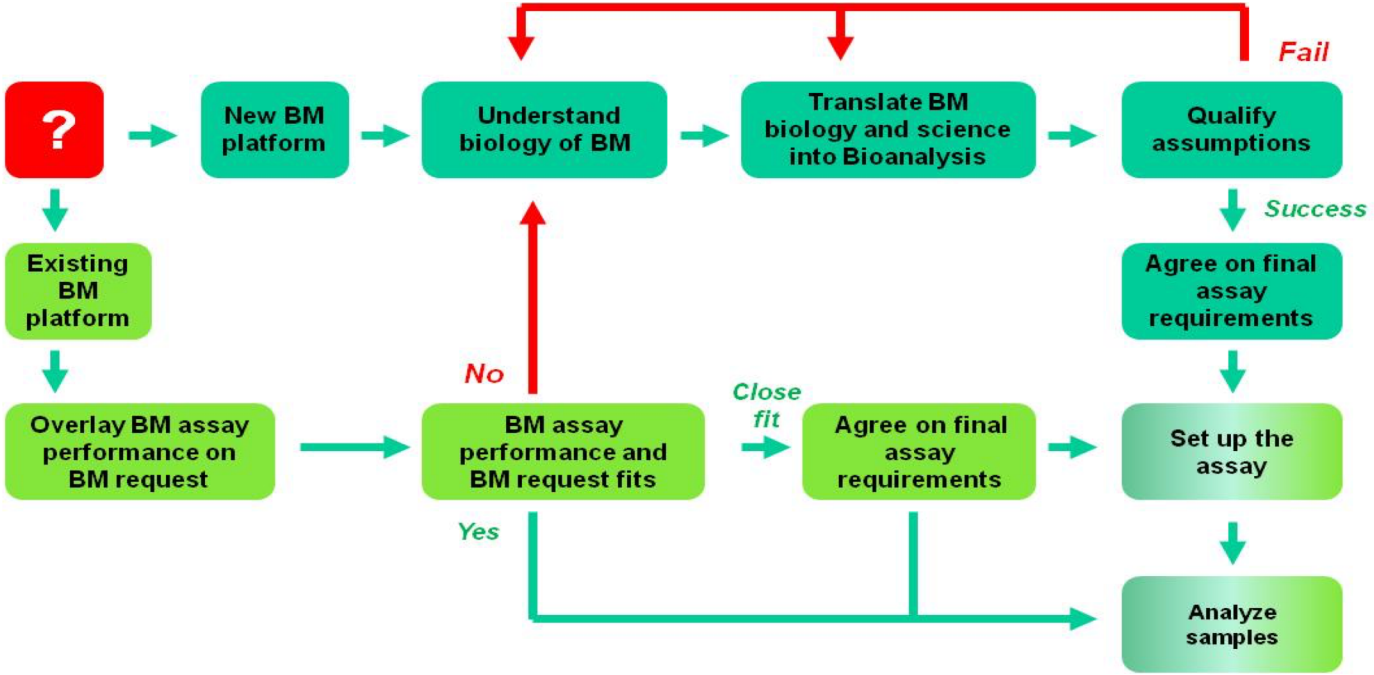
What is Context of Use for BM Assays?

- **Detailed definition of the purpose** of the assay for each analyte
  - Understood and agreed upon by all stakeholders
  - Documented in method summaries, validation plans, validation reports

- **What does it look like?:**
  - Few sentences defining biomarker assay purpose, to ensure the right assay is implemented with the appropriate level of characterisation and validation.
- Key thoughts: To understand the biology, pharmacological effect; to understand what the data will be used for, eg. scientific or safety decisions taken, to then consider what is possible from a BA perspective; to understand biological, analytical variability…
- **Ultimately:** To ensure the appropriate interpretation of data to serve patients.

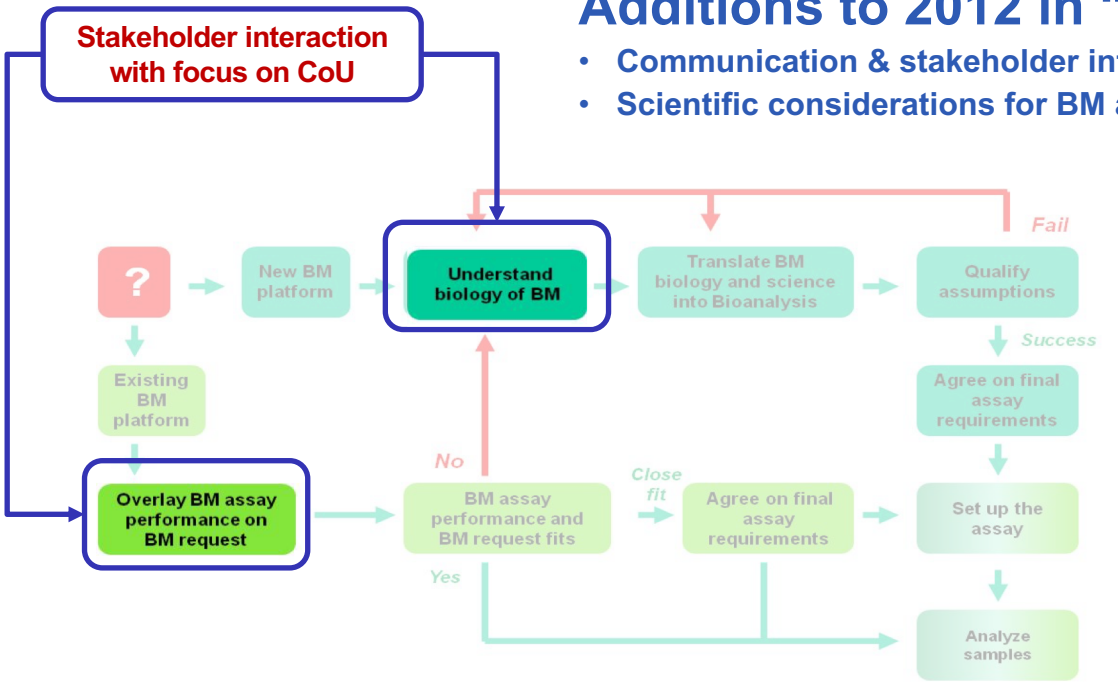
- What does it not look like?:
  - „To quantify the analyte“

EBF Recommendation 2012



Additions to 2012 in “2020 Recommendation”

- Communication & stakeholder interaction
- Scientific considerations for BM assay in CoU world

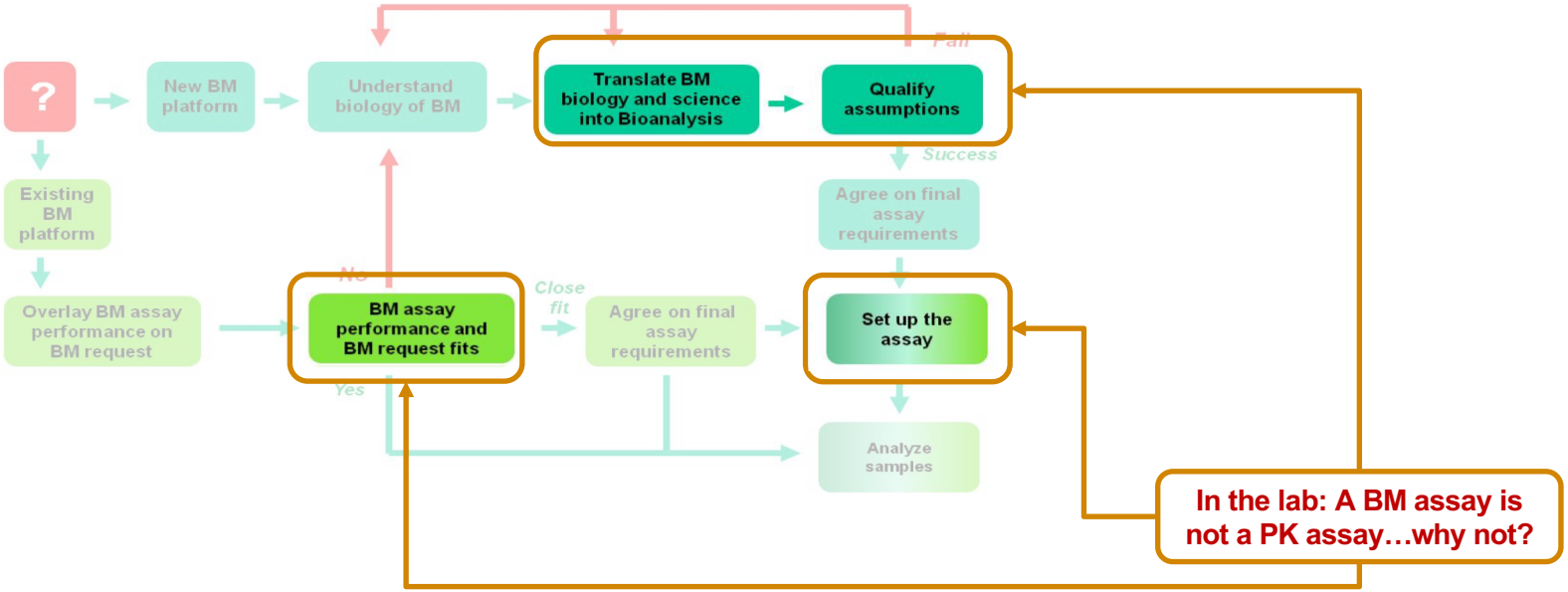


Highlights from EBF 2020 Recommendations – 1/2

- **Communication is KEY, and must be sustained.**
  - Major challenge, given organizational structures and perceptions
- **Know your stakeholders and involve them.**
  - Understanding the complexity of matrix environment, mapping is critical
  - Program Leads, Project Managers, Safety, Pharmacologists, Modelers, etc.
- **Agree on and document the COU.**
  - Implement the right assay for the right data and the right decisions
  - May require some high level, appropriate training to gain common ground

Additions to 2012 in “2020 Recommendation”

- Communication & stakeholder interaction
- Scientific considerations for BM assay in CoU world



Highlights from EBF 2020 Recommendations – 2/2

- **A BM Assay is NOT a PK Assay: Why Not?**
  - Challenges, both scientific and analytical
  - Scientific: expression levels, endogenous forms, variability, sample collection
  - Analytical: Technological advances, platforms available, kits or de novo, PK versus biomarker assay expertise, etc.

  Plus: Analytical variability and the achievable precision for an assay will be affected by assay platform and reagent choices.

- **Differences from PK assays**
  - Infinite COU‘s
  - Starting material (Endogenous vs. Recombinant, Platforms, reagents, kit);
  - Development and Validation: Parameters, Acceptance criteria
  - Regulatory Guidances: Limited

Bottom Line: Agreement across the team and documentation of the COU

A BM Assay is NOT a PK Assay: Development and Validation?

The context is ever-changing…

…but key ingredients stay the same:

- **Development (new assay), Characterization (existing assay), Feasibility (testing with known COU)**: more or less constant experiments (depending on analytical technique), independent of COU:
  - Parallelism (Selectivity, MRD, LLOQ)
  - Specificity
  - Detectability in target matrix

- **Validation:** a “rubber stamp”, based on previous assay characterization, and not equal to development.
  - Validation purely confirms, in a controlled environment, what is already known from the experiments conducted in method development.

EBF Recommendations on BM Assay Characterisation

COU must first be defined and agreed upon by all stakeholders:

- **EBF recommends** that the requirements for assay characterization occurs, and is agreed upon, as part of the COU conversation with the relevant stakeholders.

Key Topics to include:

- Type of assay required (e.g. free or total, in-house assay, commercial kit, single analyte, multiplex, research use, diagnostic)
- Format of the assay and critical reagents
- Technology choice, with pros and cons
- Do you have access to biomarker samples that are reflective of the subjects (e.g. commercial or samples from other trials, biobank)?

EBF Recommendations on BM Assay Characterisation

Several BM assay-specific parameters should be evaluated early on:

- Precision: one aspect - biological variability in population, as well as analytical variability present within the assay.
- Parallelism, selectivity, specificity, stability and sample processing must be equally evaluated.

EBF does not recommend definitive terms for dividing up into differing purposes, which may result in inappropriate regulatory hurdles being created around biomarker validation.

- Avoid categories or buckets for BM assays when starting with method development:

The term “fit for purpose” or “qualified” rather than “fully validated” can create a perspective that the quality of the assay is somehow inferior. However, in practice this is not the case.

Why is Documenting CoU for BM Assays Important?

- **The purpose of the assay may change from one study to the next**
  - The types of decisions being made based on the results may vary and should be communicated each time
  - Without an agreed COU there is a risk of implementing the wrong assay, with inappropriate characterizations and therefore validation
  - Leads to incorrect data and decisions, negatively impacting patients

- **Institutional knowledge may change:** new team members, people may leave

Bottom Line: Bioanalytical scientist takes ownership and accountability to communicate with their stakeholders and provide adequate education.

Recognising the full challenge: Game-changer

Cross-Industry Implementation of COU for patients

Omission of COU for Biomarker Assays is Dangerous

- Wrong COU: inappropriate acceptance criteria, poor use of resources and time, wrong decisions, failed drug development.
- COU must be re-evaluated as the „purpose“ changes, will dictate assay characterization and much later validation.
  - Decisions need to be driven by the science, not a framework or categories.

COU is everything, and may change over time

- Diversity and complexity of biomarker assays is wide, a framework may stifle the crucial conversations that are needed for defining the assay purpose.

Therefore: default to the misapplication of PK approaches and criteria is wrong

Learnings from 2019, and 2020, and again:

- 2020-FW workshop reconfirmed the community struggles to apply COU
- Hurdles didn't change
  - Difficult to identify or get stakeholder/end-user engaged
  - Fear for 483
  - Fear to leave the PK SOP-comfort zone

2021 bioanalytical community poll: still struggling…

1. **No proper guidance available** to understand what is expected for the various use cases
2. **Convincing stakeholders of applying the COU** process and receiving the correct feedback from stakeholders
3. Sponsors tend to think in terms of **broad categories** (exploratory & primary and secondary end point).
4. The expectation is that an **off the shelf commercial kit or prior validated method will meet** the requirements of the biomarker measurement.

This is a game-changer: what can we do…

Examples of feedback from Pharma, Biotech, CROs 2021

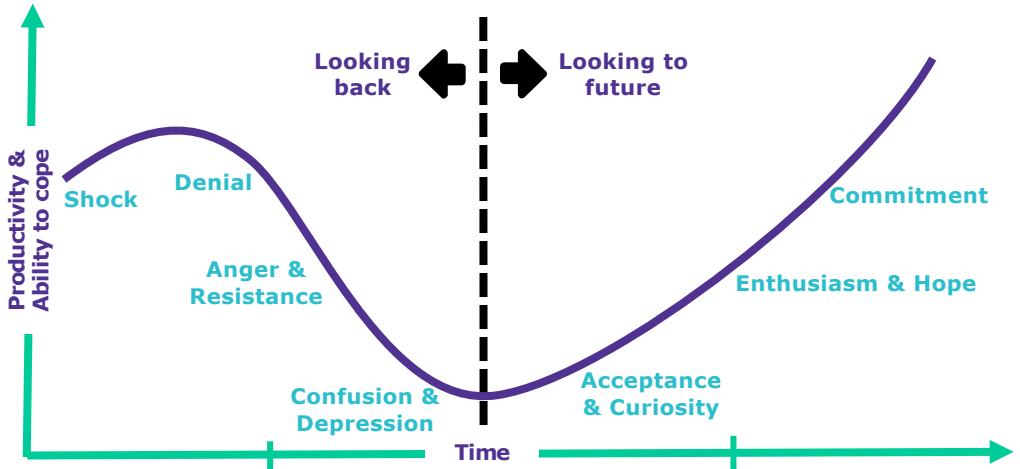
CoU Communication

1. Getting from fluffy terms to a working document that can be shared with different areas
2. No proper guidance available to understand what is expected for the various use cases
3. Convincing stakeholders of applying the CoU process and receiving the correct feedback from stakeholders
4. Internal pressures (fear of 483)
5. Communication, roles and responsibilities in R&D
6. Getting the detail for COU from the sponsor at the contracting stage to understand the purpose of the biomarker measurements
7. Convincing that FFP validation = Full validation
8. Sponsors are still having a PK mindset for both assay validation and sample analysis

CoU Analytical

1. Choosing the validation parameters and the acceptance criteria
2. Deciding the level and extent of validation of assays that are already implemented in laboratories.
3. Making sure the correct species is detected and having a proper validation guidance for the various potential uses of a biomarker
4. Understanding regulators expectations, especially for late phase/critical data
5. Making sure everyone (internally, externally) does not automatically fall back into doing PK validation experiments and using PK acceptance criteria
6. Still ticking boxes according to BMV guidelines for BM
7. Lack of understanding of the biology of the biomarker.and the limits of the analytical platforms

How do we react to change?



Every transition begins with an ending, a loss. People leave behind the way things were – and the way they themselves were in the previous situation.

A confusing in-between state. People are no longer who and where they were, but are not yet who and where they're going to be. This state can be very distressing but it also provides many opportunities.

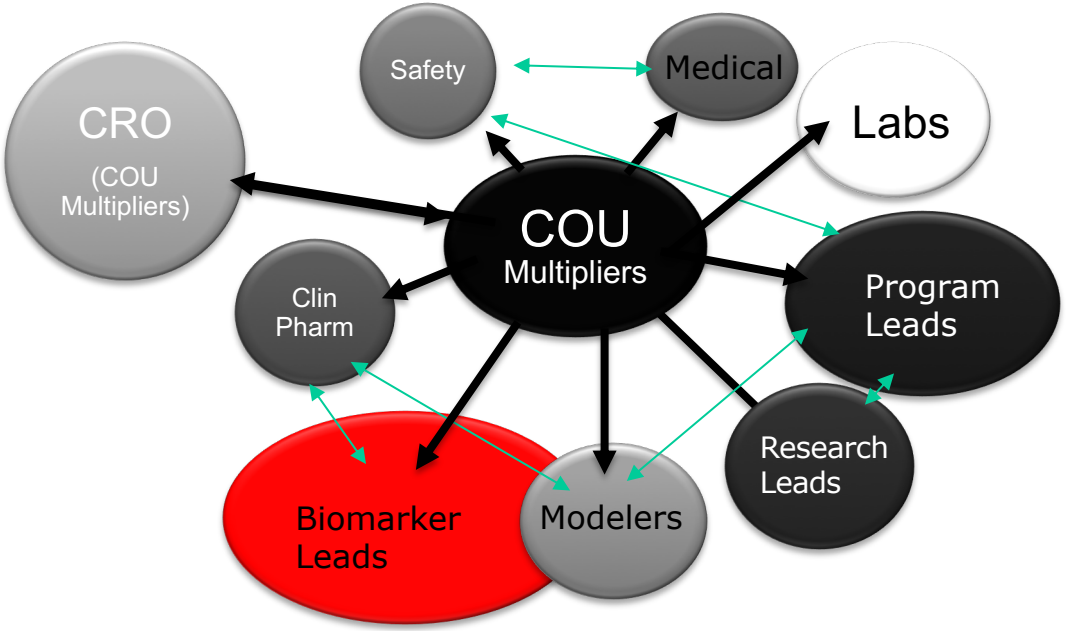
A new beginning can only happen after people let go of the past. In this phase, people accept the reality of the change and start to identify with their new situation.

Everybody can show a different emotional response to change. This response depends on a person's mind-set and which transition phase the person is in.

Understanding and identifying these individual differences is key when managing change. Unless the whole transition is managed, change will not be successful.

Changing the mindset

Truly matrix approach to communication

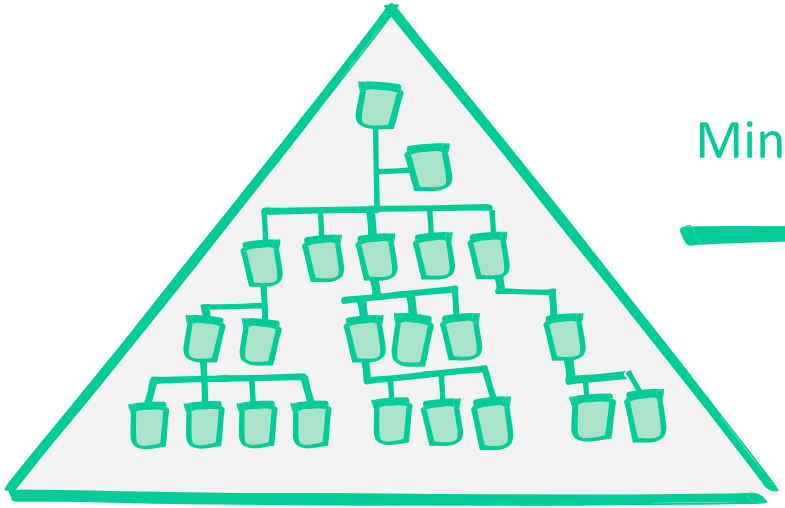


Stakeholder Management is key:

- How can we ensure COU is implemented?
- What is missing in the communication?
- How can we best educate/train?
- How can we make sure we are relaying the right message?
- How do we relay a sense of urgency for COU?
- How do we ensure consistent buy-in?

New Biomarker Strategy: implementing COU

Working cross-site, cross-functionally



Mindset

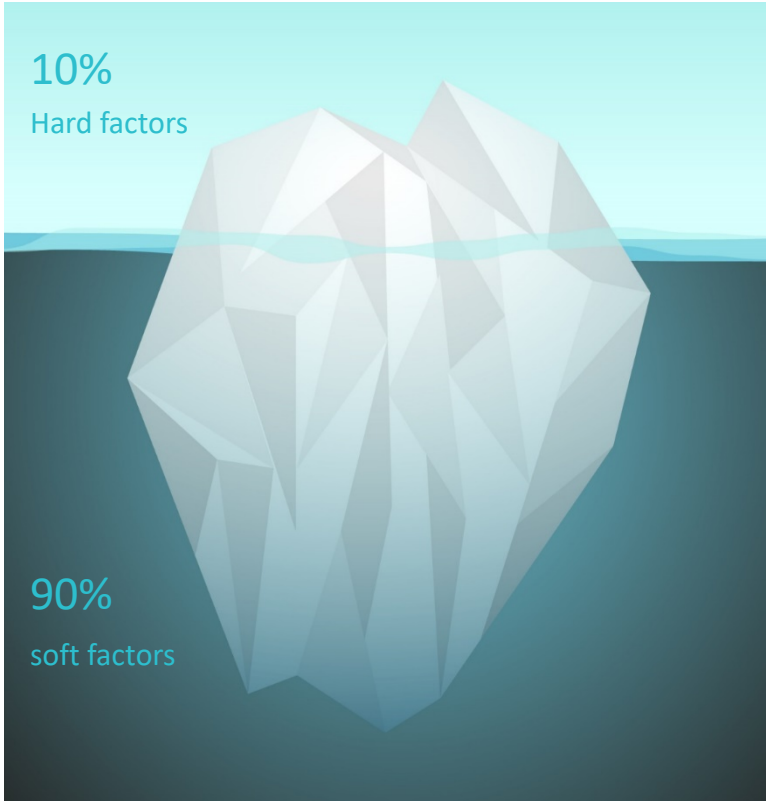
Communicate, collaborate from the beginning, throughout the lifecycle of the molecule

The iceberg model

What are key factors to make a change project successful?

- Training programs
- Costs
- Timeline
- Organizational structure
- Performance evaluation

- Involving the employees/stakeholders
- Honest and timely communication
- Emotions
- Top management commitment
- Motivating organizational culture
- Change promoters (Change Agents)
- Corporate culture of continuous change



Conclusion

The base of change management lies below the surface of the iceberg. Involving the stakeholders and an honest and timely communication is key to make a change project successful.

Next Steps

Building from BM FW April 27-28 on COU

- **We need to keep the momentum going**
  - Still have issues with understanding/alignment within BA space of what COU is, how to get the COU information right, and how that directly affects what is done in the lab, let alone stakeholder management.
  - AAPS OSD May 11: Putting Biomarker Assay Validation in Context (of Use) – Real World Challenges and Solutions – still not getting through…
  - Every BM assay is "fully validated" for the COU: need for harmonisation
- **EBF BM Strategy now and beyond** (EBF Team, YSS, Open Symposium, further FWs, **YOU**)
  - You are the multipliers of the message for COU throughout industry, to drive the topic internally and externally
  - How do we avoid inappropriate guidance from HAs, inappropriate implementation of BMV guidance on BM assays in general
  - How do we change the way of thinking – this is not repackaging of the Jean Lee or subsequent FFP papers – rather diving deeper into the strategy and the science that supports COU implementation.
- **Clarity and alignment across industry**

Biomarker Assay COU: The Game-Changer

- **Understand what it is**
- **Understand why it is critical**
- **Understand how to implement it, considering the many challenges**
  - Scientific
  - Analytical
  - Stakeholder management